Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-7, 9-10, 12-13, and 82-86 are pending in this application, with claims 1, 12-13 and 85 being independent claims.

Claims 1, 12 and 13 are being amended without prejudice or disclaimer.

Claims 85 and 86 are new.

Support for these claim amendments may be found in the in the original claims (e.g., claim 81) and in the specification, for example, at least in paragraphs 0021-0023, 0045-0046, 0053, and 0058-0059, and figures 4-10 (mutants); paragraphs 0112 and 0084-0095 (derivatives of betulin, betulinic acid, oleanolic acid, pomolic acid, ursolic acid, and platanic acid); and paragraph 0118 (pharmaceutically acceptable salts).

The specification has been amended to correct an obvious typographical error in the spelling of "pomolic acid." The correction of an error is not new matter if both the error and its correction would have been readily apparent to one of ordinary skill in the art. Additionally, support for the correction is found in a publication cited in paragraph 0084, Kashiwada et al. (*J. Nat. Prod. 61*:1090-1095 (1998) (IDS Document AS5), which correctly spells "pomolic acid" in the title.

It is believed that these changes introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and further request that they be withdrawn.

References Cited by Examiner

Applicants thank the Examiner for forwarding copies of the cited non-patent literature references via email.

Request for Examiner Interview Prior to Next Office Action

This Amendment and Reply is being filed with a Request for Continued Examination. Applicants respectfully request an interview after the Examiner has considered this paper and prior to the issuance of a new Office Action. The issues to be discussed are the rejections of any pending claims under 35 U.S.C. § 112, first paragraph for alleged lack of written description and enablement.

Rejections Under 35 U.S.C. § 112, Written Description

The rejection of claims 1-7, 9-10 and 82-84 for allegedly failing to comply with the written description requirement was maintained. Paper No. 20070920, p. 3. Applicants respectfully traverse this rejection.

Applicants have amended claim 1 to recite that the compound being administered is a derivative of betulin or betulinic acid. The specification clearly contemplates the use of derivatives of betulin and betulinic acid, for example, in paragraphs 0084-0095. Therefore, the inventors had possession of the subject matter of claims 1-7, 9-10 and 82-84, and these claims are fully supported by the written description. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

The specification also clearly contemplates the use of a genus of related triterpenoid compounds in paragraphs 0012 and 0084. For example, in paragraph 0084, the specification states:

> Compounds useful in the methods of the present invention include derivatives of betulinic acid and betulin that are presented in U.S. Patent Nos. 5,679,828 and 6,172,110 respectively, and in U.S. application Nos. 60/443,180 and 10/670,797, which are herein incorporated by reference. Additional useful compounds include oleanolic acid derivatives disclosed by Zhu *et al.* (*Bioorg. Chem Lett. 11*:3115-3118 (2001)); oleanolic acid and promolic acid derivatives disclosed by Kashiwada *et al.* (*J. Nat. Prod. 61*:1090-1095 (1998)); 3-*O*-acyl ursolic acid derivatives described by Kashiwada *et al.* (*J. Nat. Prod. 63*:1619-1622 (2000)); and 3-alkylamido-3-deoxy-betulinic acid derivatives, disclosed by Kashiwada *et al.* (*Chem. Pharm. Bull. 48*:1387-1390 (2000)). (All references incorporated by reference).

Specification, ¶ 0084. Thus, the specification describes the use of all the compounds recited in claims 85 and 86. Moreover, as is discussed below in reference to the enablement rejection, these recited compounds are structurally related to derivatives of betulin and betulinic acid in that they are all triterpenes (also known in the prior art as triterpenoids). As seen on the attached **Exhibit A**, triterpenes share a common core structure in their backbone of four fused six-carbon rings. Since they all belong to the same genus of triterpene compounds, the description of derivatives of betulin and betulinic acid also supports the compounds recited in claims 85 and 86. Therefore, for all of these reasons, the inventors had possession of the subject matter of new claims 85 and 86. Accordingly, these claims are fully supported by the written description.

Rejections Under 35 U.S.C. 112, First Paragraph, Enablement

The rejection of claims 1-7, 9-10 and 82-84 for allegedly failing to comply with the enablement requirement was maintained. Paper No. 20070920, p. 4. Applicants respectfully traverse this rejection.

As discussed above, Applicants have amended claim 1 to recite that the compound being administered is a derivative of betulin or betulinic acid. The Amendment and Reply filed July 18, 2007 presented evidence that PA-457 and PA-040 have entered into FDA-approved clinical trials for treatment of HIV-1 infection. These compounds are derivatives of betulinic acid or betulin. Therefore, claims 1-7, 9-10 and 82-84 are enabled. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

In addition, new claims 85 and 86 recite that the compound being administered is a derivative of oleanolic acid, pomolic acid, ursolic acid, or platanic acid. Applicants submit that the evidence of enablement presented in the Amendment and Reply filed July 18, 2007 is also relevant to claim 85 because PA-457 and PA-040 are structurally related to derivatives of oleanolic acid, pomolic acid, ursolic acid and platanic acid, in that they are all triterpenenes. *See*, for example, Lee and Morris-Natschke, *Pure Appl. Chem. 71*:1045-51 (1999) (IDS Document NPL22) ("Betulinic acid, a triterpene isolated from *Syzigium claviflorum*, was active against HIV replication. . . . The related platanic acid has an acetyl rather than an isopropenyl side chain" and "[t]wo other natural triterpenoids from *Rosa woodisii*, *Hyptis captitata*, and other species, oleanolic acid and pomolic acid. . ." (citations omitted), at p. 1046; and Baglin et al., *Mini Rev. Med. Chem. 3*:525-39 (Sept. 2003) ("The aim of this review is to update current knowledge on the

betulinic, ursolic and echinocystic acids and their natural and semisynthetic analogs, focussing [sic] on their cytotoxic and anti-HIV activities. Then, the last results of the authors' team on unusual semisynthetic derivatives of these triterpenoids will. . .") (abstract attached as **Exhibit B**); *see also* **Exhibit A**. In addition, Lee and Morris-Natschke conclude by saying, "[i]n summary, . . . the betulinic acid derivatives DSB and DSD, as well as their related compounds, have exciting potential as anti-HIV chemotherapeutic agents." Therefore, because derivatives of betulinic acid, oleanolic acid, pomolic acid, ursolic acid and platanic acid are triterpenenes, one of ordinary skill in the art would find the evidence already of record for PA-457 and PA-040 to be relevant to other triterpenoids such as those recited in claims 85 and 86. Therefore, claims 85 and 86 are also enabled.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Applicants respectfully request an interview with the Examiner to discuss any outstanding rejections once she has had the opportunity to consider the present amendment and response.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Helene C. Carlson
Agent for Applicants
Registration No. 47,473

Date: October 31, 2007

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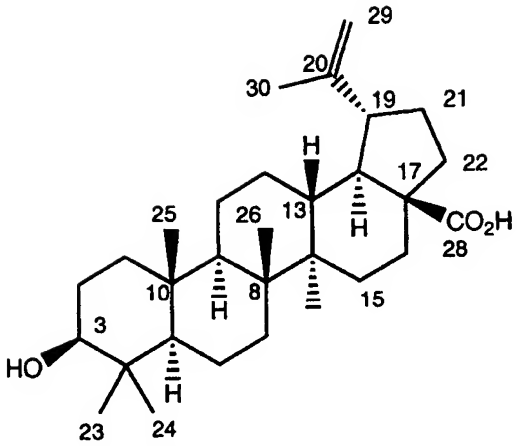
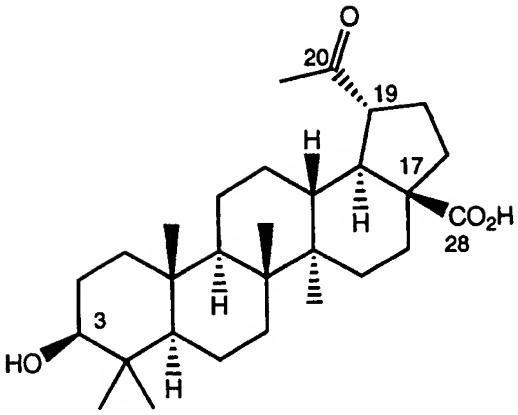
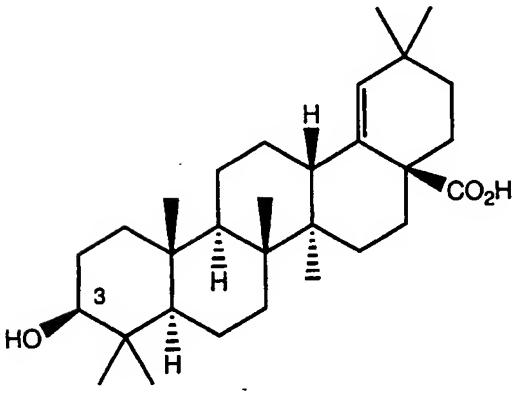


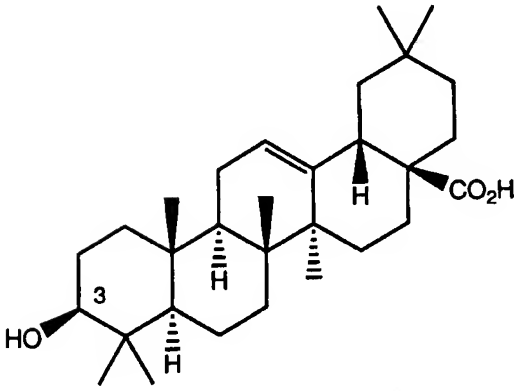
Betulinic Acid
EC_{50} 1.4 μM
IC_{50} 13 μM



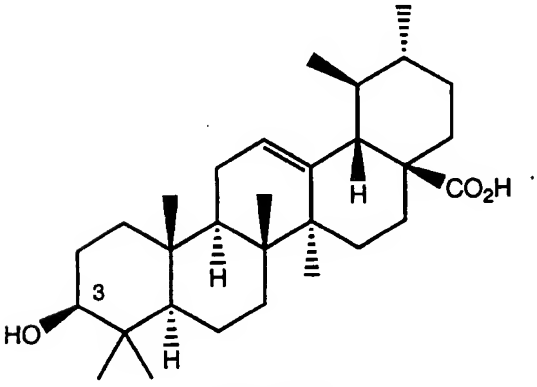
Platanic Acid
EC_{50} 6.5 μM
IC_{50} 90 μM



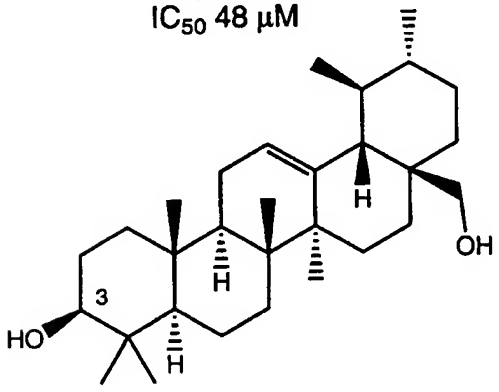
Morolic Acid



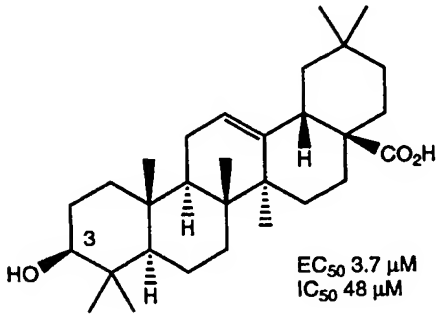
Oleanoic Acid
EC_{50} 3.7 μM
IC_{50} 48 μM



Ursolic Acid
EC_{50} 4.4 μM
IC_{50} 14 μM

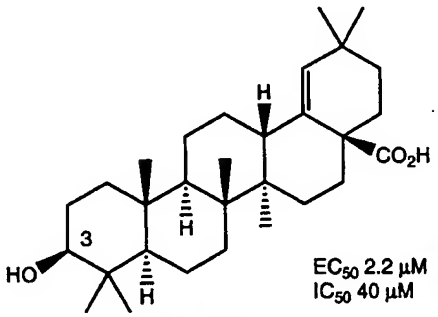


Uvaol



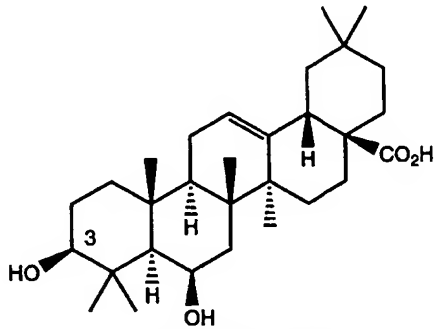
EC_{50} 3.7 μM
IC_{50} 48 μM

Oleanolic Acid
3-Hydroxy-(3β)-olean-12-en-28-oic Acid

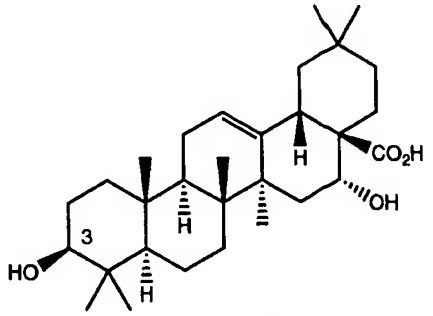


EC_{50} 2.2 μM
IC_{50} 40 μM

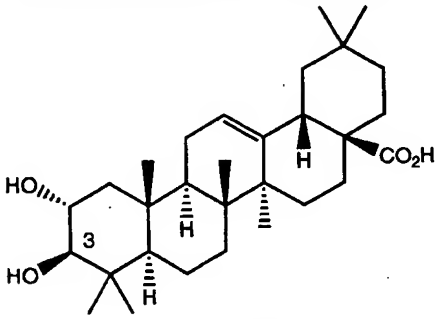
Morolic Acid
3-Hydroxy-(3β)-olean-18-en-28-oic Acid



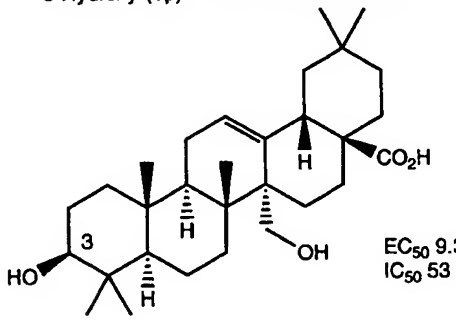
Sumaresinolic Acid
3,6-Dihydroxy-(3β,6β)-olean-12-en-28-oic Acid



Echinocystic Acid
3,16-Dihydroxy-(3β,16α)-olean-12-en-28-oic Acid

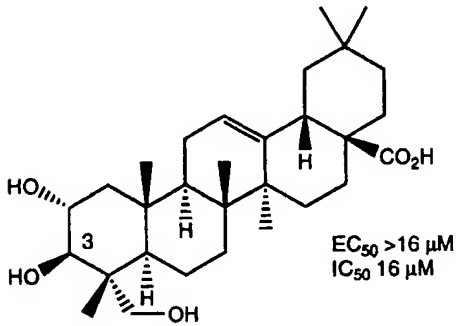


Maslinic Acid
2,3-Dihydroxy-(2α,3β)-olean-12-en-28-oic Acid



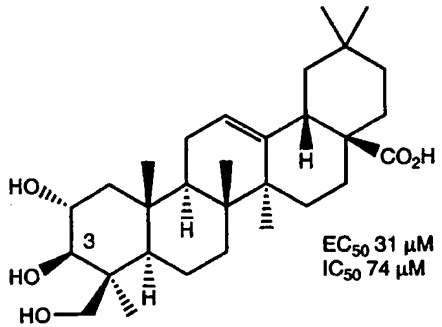
EC_{50} 9.3 μM
IC_{50} 53 μM

3,27-Dihydroxy-(3β)-olean-12-en-28-oic Acid



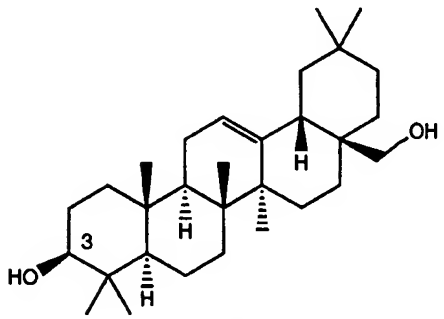
EC_{50} >16 μM
IC_{50} 16 μM

Hyptatic Acid
2,3,23-Trihydroxy-(2α,3β,4α)-olean-12-en-28-oic Acid

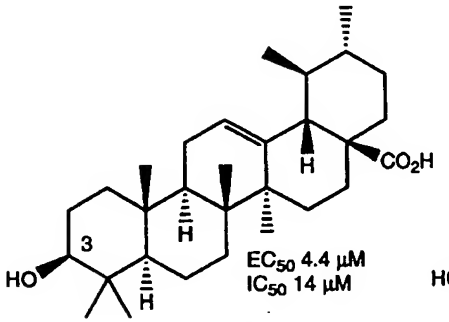


EC_{50} 31 μM
IC_{50} 74 μM

Arjunolic Acid
2,3,24-Trihydroxy-(2α,3β,4β)-olean-12-en-28-olc Acid



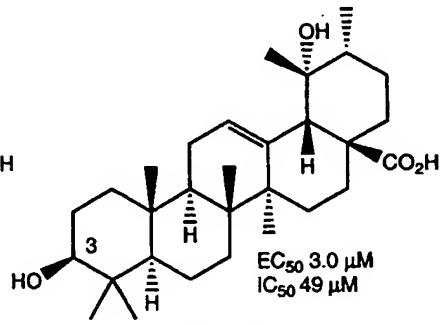
Erythrodiol
(3β)-Olean-12-ene-3,28-diol



EC_{50} 4.4 μM
IC_{50} 14 μM

Ursolic Acid

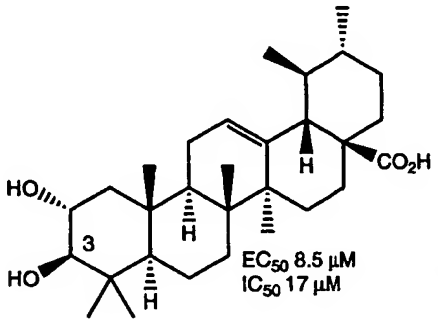
3-Hydroxy-(3β)-urs-12-en-28-oic Acid



EC_{50} 3.0 μM
IC_{50} 49 μM

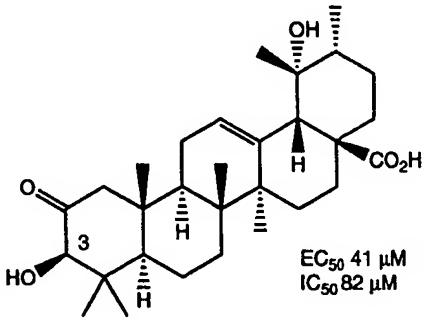
Pomolic Acid

3,19-Dihydroxy-(3β,19α)-urs-12-en-28-oic Acid



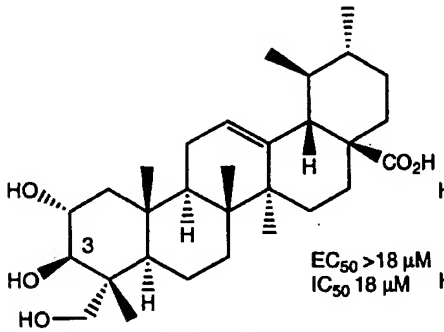
EC_{50} 8.5 μM
IC_{50} 17 μM

2,3,-Dihydroxy-(2α,3β,)-urs-12-en-28-oic Acid



EC_{50} 41 μM
IC_{50} 82 μM

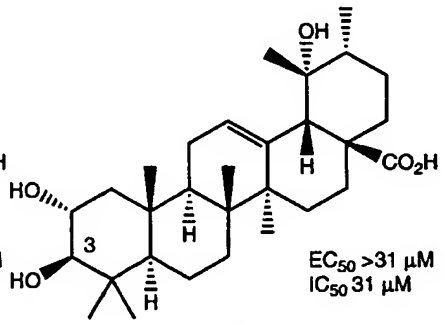
3,19-Dihydroxy-2-oxo-(3β,19α)-urs-12-en-28-oic Acid



EC_{50} >18 μM
IC_{50} 18 μM

Asiantic Acid

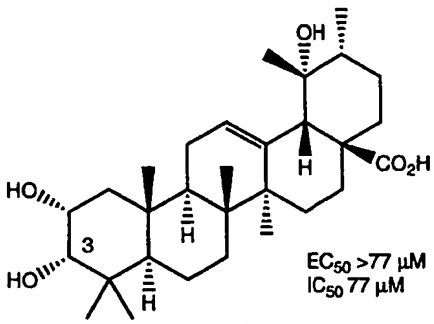
2,3,23-Trihydroxy-(2α,3β,4α)-urs-12-en-28-oic Acid



EC_{50} >31 μM
IC_{50} 31 μM

Tormentic Acid

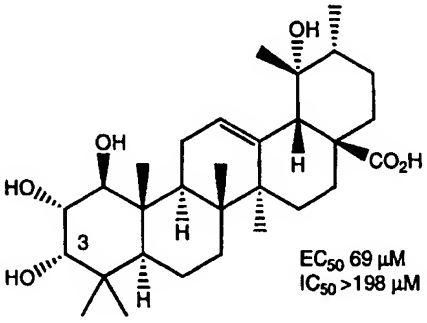
2,3,19-Trihydroxy-(2α,3β,19α)-urs-12-en-28-oic Acid



EC_{50} >77 μM
IC_{50} 77 μM

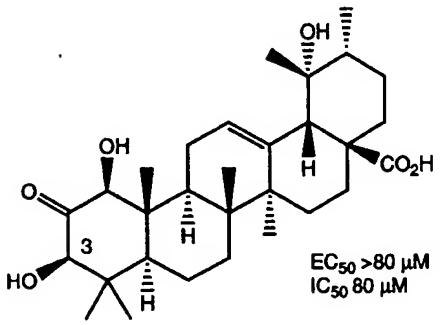
Euscaphic Acid

2,3,19-Trihydroxy-(2α,3α,19α)-urs-12-en-28-oic Acid



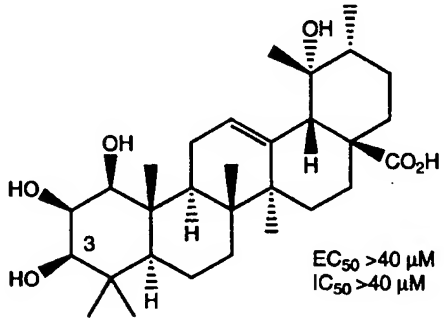
EC_{50} 69 μM
IC_{50} >198 μM

2,3,19-Trihydroxy-(2α,3α,19α)-urs-12-en-28-oic Acid



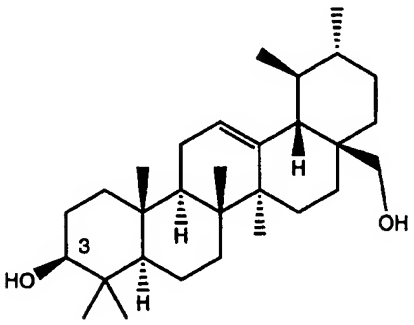
EC_{50} >80 μM
IC_{50} 80 μM

1,3,19-Trihydroxy-2-oxo-(1β,3β,19α)-urs-12-en-28-oic Acid



EC_{50} >40 μM
IC_{50} >40 μM

1,2,3,19-Tetrahydroxy-(1β,2β,3β,19α)-urs-12-en-28-oic Acid



Uvaol

1: Mini Rev Med Chem. 2003 Sep;3(6):525-39.

A review of natural and modified betulinic, ursolic and echinocystic acid derivatives as potential antitumor and anti-HIV agents.

Baglin I, Mitaine-Offer AC, Nour M, Tan K, Cavé C, Lacaille-Dubois MA.

Unité MIB, JE 2244, Faculté de Pharmacie, Université de Bourgogne, 7 Bd Jeanne d'Arc, BP 87900, 21079 Dijon Cedex, France. malacd@u-bourgogne.fr

The aim of this review is to update current knowledge on the betulinic, ursolic and echinocystic acids and their natural and semisynthetic analogs, focussing on their cytotoxic and anti-HIV activities. Then, the last results of the authors' team on unusual semisynthetic derivatives of these triterpenoids will be presented in order to establish structure/activity relationships.

PMID: 12871156 [PubMed - indexed for MEDLINE]